

Remarks. The applicants request entry of the present amendment and reconsideration of the claims. Claims 2, 3, 6-8, 17-21, 30 and 31 are pending. Each amended and new claim has written support in the specification; accordingly, no new matter has been added to the application.

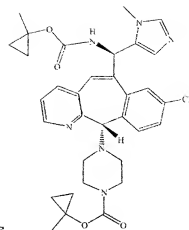
The amendment to claim 17 makes only minor, formal changes which clearly do not add new matter

Written support for new claims 30 and 31 appears in the specification, for example, at page 6, lines 8-9.

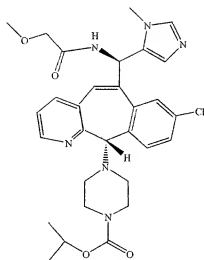
Claims rejections under 35 U.S.C. § 112(¶1)-written description. Claim 18 stands rejected as allegedly lacking written description. The examiner took the position that the two compounds specified in claim 18 are not described in the specification. The Applicants disagree. In general, regarding claims reciting chemical compounds, the written description requirement requires that the structure of the compound be described sufficiently that one may conclude that the applicants had possession of the compound at the time of invention. The compounds specified in claim 18 are described in claim 18 as filed. A claim provides written description for itself. Claim 18, as filed, clearly describes the complete chemical structure of two compounds and should be deemed compliant with the written description requirement. The Applicants request withdrawal of the rejection.

Claims rejections under 35 U.S.C. § 112(¶1)-enablement. Claims 9-16 and 22-29 stand rejected as allegedly lacking an enabling disclosure in the specification. Since these claims have been cancelled, this rejection is moot.

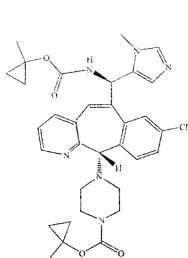
Claim 18 also stands rejected as allegedly lacking an enabling disclosure. The examiner alleged that a practitioner would have been required to engage in undue amounts of



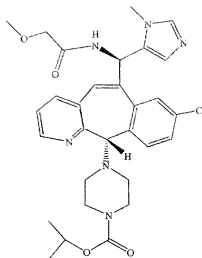
experimentation to make and use compounds



and . The applicants submit that the compounds in claim 18 could have been used in the same manner in which compounds 1-81 could have been used. As pointed out by the examiner in the April 19, 2007 office action, claims covering use of any of compounds 1-81 are enabled (see page 4). All of these compounds, comprising the same tricyclic core structure, are *highly* structurally related and can be made and used in an equally related manner. The fact that there is some structural diversity among the compounds is not probative of any lack of enablement. Given the high degree of structural similarity among the compounds, it would be readily apparent to any practitioner of ordinary skill in the art that



; and



may be used,

e.g., in the claimed methods of treatment, in essentially the same manner as that of any of compounds 1-81. Tricyclic FTIs have been known in the art and the focus of extensive commercial and academic interest for over a decade. The chemical arts in the area of tricyclic FTIs has matured to the point that synthesis of any of the derivatives in claim 18 would have been simple. For example, synthesis of the compounds of claim 18 is discussed in PCT application publication no. WO2005/014577.

Withdrawal of all rejections for lack of enablement is appropriate and is hereby requested.

Claims rejections under 35 U.S.C. § 112(f)(2). Claim 17 stands rejected as allegedly indefinite because the term "the level of Ca^{2+} " has no antecedent basis. The applicants point out that this term is no longer in claim 17, as amended.

Claims 10 and 23 also stand rejected for alleged indefiniteness. Since these claims have been cancelled, this rejection is moot.

The applicants request withdrawal of all rejections for alleged indefiniteness.

Claims rejections under 35 U.S.C. § 103(a). Claims 2-3 and 6-29 stand rejected as allegedly obvious over Doll et al. (WO 97/23478), Pearl et al. (Oncology Update (1996) 3(5):163-

166) and the Merck Manual of Diagnostics Home Edition ((1997) pp. 738-739). Since claims 9-16 and 22-29 have been cancelled, this rejection, with respect to those claims, is moot. The rejection of claims 9-16 and 22-29, under § 103(a), will not be addressed. The examiner argued that Doll et al. discloses that the compounds of formulas 1-81 may be used to treat various types of cancer; that Pearl et al. discloses that patients with various types of cancer are likely to have hypercalcemia of malignancy; and that the Merck Manual discloses also that patients with cancer may also suffer from hypercalcemia. The examiner further argued that it would have been obvious to treat hypercalcemia of malignancy in cancer patients with a compound of formula 1-81 "since hypercalcemia of malignancy is often present in breast and lung cancers as well as in cancers in general." The applicants disagree. The claims are patentable over the cited art.

As pointed out by the Supreme Court, in an obviousness analysis, the examiner must "identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements [in the cited prior art] in the way the claimed new invention does." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007). The Applicants submit that such a reason did not exist at the time of the present invention. Moreover, the prior art can be modified or combined to reject claims as *prima facie* obvious as long as, in making the modification or combination, there is a reasonable expectation of success in achieving the claimed invention. *In re Merck*, 800 F.2d 1091 (Fed. Cir. 1986). In this case, in view of the prior art, a practitioner would not have had any reasonable expectation of success in using any of compounds 1-81 for the treatment of a disorder of calcium homeostasis.

The fact that a compound represented by any of formulas 1-81 (compounds 1-81) is effective at treating cancer does not

suggest that it would have also been effective at treating disorders of calcium homeostasis, such as hypercalcemia of malignancy, or, for that matter, any other disease that is also commonly suffered by cancer patients. This point was touched on during the July 12, 2007 telephone discussion between the undersigned and examiners Issac and Jiang. There is no indication in the cited art that compounds represented by any of compounds 1-81 exhibited a "class effect" which, via a common molecular mechanism, led to a beneficial effect respecting both cancer and calcium homeostasis disorders. Specifically, farnesyl protein transferase inhibitors (FTIs), such as compounds 1-81, exert their anti-cancer effect through inhibition of farnesyl protein transferase. The downstream anti-cancer effects of FTI were once suspected to have been mediated via Ras; however, this point is presently uncertain. The cited art does not indicate whether compounds 1-81 have their effect on calcium homeostasis also via inhibition of farnesyl protein transferase. Indeed, the specification states that the effect of compounds 1-81 may be mediated through modulation of the calcium sensing receptor (see e.g., page 27, line 21 to page 28, line 7). Furthermore, Example 2 in the specification suggests that compounds 1-81 effect the physiology of and, thus, may mediate their effects on calcium homeostasis via, the parathyroid gland. Thus, there would have been no reason for a practitioner to have assumed that disorders of calcium homeostasis, such as those recited in the claims, were mediated via farnesylation or Ras and have tried using FTIs for such disorders. In short, the claimed methods represent an utterly and completely new use of a known compound which could not, in any way, have been predicted by consultation of the cited art.

Claims 9-16 and 23-29 stand rejected as allegedly obvious over Doll et al. (WO 97/23478) in view of Eskins et al.

(Cancer Treatment Rev. (2000) 26:319-332) in further view of the statement in the specification at page 3, lines 8-15 and in further view of Nemeth *et al.* (Proc. Natl. Acad. Sci USA (1998) 95(7): 4040-4045). Since claims 9-16 and 23-29 have been cancelled, this rejection is moot.

The applicants submit that withdrawal of all claim rejections for obviousness is appropriate and request such action.

Conclusion.

The claims are in condition for passage to allowance. Such action is earnestly solicited. The examiner is invited to contact the undersigned should there be any outstanding questions or concerns regarding the present application.

Respectfully submitted,

Date: Dec. 7, 2007



Thomas Triolo, Ph.D., J.D.
Registration No. 48,001
Attorney for Applicant(s)

Schering-Plough Corporation
Patent Department; K-6-1, 1990
2000 Galloping Hill Road
Kenilworth, NJ 07033
908-298-2347